Editorial

Anaesthetic research in low- and middle-income countries

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In this issue of *Anaesthesia*, Kwikiriza et al. [1] report a randomised controlled trial comparing the analgesic effects of intrathecal morphine with ultrasound-guided transversus abdominis plane block after caesarean section at a Ugandan Regional Referral Hospital. The publication of this study, authored by an international team, represents an important example of the role of academic anaesthesia in global health.

Anaesthesia has a long history of publishing studies relating to the state of anaesthesia provision in low- and middle-income countries (LMICs). In 1964, the Association of Anaesthetists chaired a meeting in London to discuss the anaesthetic problems 'confronting the peoples of the developing countries of the world', with the subsequent establishment of a subcommittee to consider these problems and make recommendations for their resolution. An excerpt from the ensuing report was published in *Anaesthesia* in 1967 – the same year that J.V. Farman reported on a Symposium held at Addenbrooke's Hospital, Cambridge, on 'Anaesthetic problems facing developing countries' [2, 3].

Today, the Association of Anaesthetists has an established International Relations Committee which aims to do the following: support anaesthetists who train, work or undertake research in LMICs; distribute educational materials and develop high-quality anaesthesia training courses; and promote access to safe surgery and anaesthesia as a public health priority. Commensurately, a search through the *Anaesthesia* archives returns hundreds of research articles, letters and opinion pieces, with various summary editorials relating to low- and middle-income anaesthesia and intensive care provision [4–6].

Research in LMICs

On closer investigation, many of these publications can be grouped into either those exploring the problems in LMICs, or those describing the delivery or evaluation of interventions led by high-income partners to improve provision [7, 8]. These interventions, rooted deeply in the concept of international aid, span equipment donation, education, checklist implementation, and service redesign [9–11]. However, the publication of relevant clinical trials, particularly with both first and senior authors from a LMIC institution, is notably largely absent.

Why should this be? The simple answer is one of resources: human, financial and institutional. The multiple stressors of a high clinical burden, low public sector pay and consequent private practice commitment, weak institutional support for research, and lack of available research funding mean that overburdened LMIC clinicians have little time to devote to research [12]. If we consider the complex system required to support anaesthetic research in the UK, both at national and local levels, it becomes obvious why resource-poverty is a huge impediment to active research.

Why does this matter? Outcomes from anaesthesia have improved globally in the past 50 years, and although these have not been evenly distributed across the world, it could be argued that the underlying basic science and clinical research necessary to inform safe anaesthesia has been done [13]. Although high-income countries rightly

continue to try to improve care quality through ongoing research, is there a place for this in settings where the anaesthetic mortality is close to 1% [14]? Some would argue that the challenge in LMICs is not what to do, but how to improve care to current high-income country standards. Indeed, the fields of implementation science, improvement science, and operational research may all be used to embed this within academically rigorous frameworks [15–18].

Impact of research on LMICs

There are two key problems with this assertion. The first is that developing research capacity in a subset of the clinical workforce is good for the overall quality of care delivered by a healthcare system. High-quality research strengthens institutions, motivates individuals, and encourages LMIC clinicians to engage internationally on level terms. Second, and crucial, is the fact that what we perceive as the 'right' way to deliver care may not translate between settings or populations [19, 20]. There is a grave risk of unintentional neo-colonialism in the assertion that richer countries have solved the problem of safe anaesthesia, and now just need to educate the poorer countries of the world. Anaesthesia is an art and a science, embedded within a complex system of care. Any improvement needs to be locally owned and locally driven, and this should begin with questions regarding the very fundamentals of that care [21].

As an example, Cambridge University Hospitals NHS Trust has a long-standing institutional partnership with Mulago Hospital and Makerere University College of Health Sciences in Uganda. This involves collaboration on basic science research through the University Departments of Pathology and the Cambridge Africa programme, which supports visiting African academics to learn research skills in Cambridge to inform their locally hosted projects. Recent collaborative work led by Dr A. Nakimuli and Professor A. Moffet has shown a genetic variation between Ugandan and British parturients with regard to the killer cell immunoglobulin-like receptors which are involved with the development of pre-eclampsia [22], while conversations during exchange visits from Ugandan anaesthetists to Cambridge have suggested that the principle presenting complaint from pre-eclampsia in their Ugandan population is type-1 respiratory failure (personal communication, Dr A. Kintu). Interestingly, this has been subsequently observed in Ugandan patients presenting to the Rosie Maternity Hospital in Cambridge. It seems reasonable to hypothesise that genetic variation, which may contribute to a different pathophysiology, may necessitate a different treatment regimen in Uganda than is common practice in the UK. Clinical improvement in this context clearly requires further basic scientific research, robust epidemiological data, pragmatic clinical trials to understand the necessary care interventions, and then a programme of improvement work to institute that care. This work benefits hugely from a collaborative international approach in a partnership of equals; that equality, however, necessitates Ugandan researchers operating on a level playing field with their Cambridge colleagues.

There are also issues related to the wider care obligations of researchers, who may uncover life-threatening medical problems in their research subjects, which are not treatable within the resources of the country where the study is taking place. Should this then demand a separate bioethics consultation as part of the research ethics [23]? Would investigators accept additional clinical responsibilities, or is the therapeutic relationship limited by time and resource limitation? Would it further constrain badly needed insights into healthcare needs in LMICs? There is certainly the need for more thoughtfully conducted studies, with improvements in programme planning, monitoring and evaluation, as well as global and/or national policies regarding foreign medical programmes [8, 24].

Supporting LMIC research

At a UK funding level, the fostering of research capacity as a tool for sustainable development is supported by recent funding available through the National Institute for Health Research (NIHR) and the Research Councils UK Global Challenges Research Fund to support academic collaboration between the UK and LMIC partners [25, 26]. Groups funded through these mechanisms, such as the NIHR Global Health Research Group on Neurotrauma, have a direct mandate to work to improve the research capacity of their LMIC partners. However, a large amount of LMIC research output occurs outside of formal academic funding structures and is born out of looser 'development' funding and volunteering. Where academic funding agencies can use fiscal muscle to determine the rules of engagement in LMIC research, this burden is passed on to journal editors when originating from outside of established academia.

Submissions such as that by Kwikiriza et al. raise a number of interesting dilemmas for an international medical journal. On a practical level these include ensuring research studies have appropriate ethical oversight and study quality and raise questions about publication fees – especially when the group in question is locally led and from a HINARI Access to Research in Health Programme Group 1 country, but co-authored by clinicians affiliated to one of the world's richest universities. On a more philosophical level, they raise questions as to the role of journals with respect to supporting LMIC clinical research, and the generalisability of that research.

Role of journals

What then is the role of major journals in fostering LMIC-based authors? One perspective might be that academic journals ought to aspire to publish only the highest quality research and, by maintaining this high standard, drive research quality from whoever it might originate. Advocates for this point of view might argue that relaxing the criteria for publication based on the setting in which a study is performed is both academically compromising and patronising. An alternative position might be to argue that, given the historical imbalances of power and funding between high- and low-income regions, the only way for LMIC authors to be encouraged and supported in building research capacity is to provide more editorial support for their submissions. This might include recognising that primary outcome measures for studies conducted may not always be relevant to a majority of their readers, and that circumstance may influence the chosen research methods in a way that would ordinarily mean the study would be rejected on methodological grounds. This is a complex argument, muddied by many factors: the role of HIC partners and research funding in the research generation; the stated aims of the journal involved; the rapid proliferation of predatory online journals and the increasing interest in global health as an academic entity – evidenced by the recent creation of specific global health offshoots of *The Lancet* and *British Medical Journal*. There is also a more fundamental issue at stake; an important way of judging the success (or otherwise) of a study is whether that knowledge has been shared with the wider scientific community – this is an obligation that unites researchers, publishers and editors of journals alike [12].

These issues necessitate careful thought. Should editors hold papers to a different account if the authors all hail from the LMIC in question as opposed to being a conglomerate of high-income country and LMIC partners? If so, then intra-country heterogeneity may also need to be accounted for, as many LMICs have a wide disparity between different centres in terms of academic experience. Furthermore, at what point does an author transition from being supported by a journal to being held to the same account as if submitting from a high-income country? This would seem odd if it was linked to the Human Development Index of their home country rather their own academic pedigree – but this then becomes a minefield for editors who are trying to ascertain whether the authors in question should be nurtured or rejected.

A further consideration is one of generalisability. Many papers claim applicability to 'LMICs' while in fact reporting local results from a given country or even a specific health centre; this may not be a fair generalisation. Where this is in the context of a high-income country/LMIC partnership, it is even more questionable, as the centre being studied may now have both skills and equipment imported as part of their partnership, which are not available outside of their centre. Should we then be moving away from the broad brushstrokes of declaring that any given result or intervention is pertinent to LMICs any more than it is pertinent to high-income countries? How do we report otherwise methodologically sound studies in a way which paints a fair picture?

The way forward

As with most complex situations, there is room for balanced pragmatism. Thresholds of both ethical oversight and data quality clearly need to be met in order for research to be justifiably published by a reputable journal, but criteria around the study description or written English may be relaxed by a journal wishing to see more 'home-grown' LMIC research and which is willing to support authors in revising their submissions. Whether journals should, as some have, demand at least one LMIC author for papers reporting data from these countries is debatable – although co-publication is obviously the aim, this should not come at the cost of tokenism, and a single named author is no guarantee of responsible academic collaboration. In reality, the decision regarding which manuscripts to accept, and how authors should be supported, will rely on the judgement of experienced editorial boards who aim to balance all of these varied factors in coming to a decision.

A more objective approach might be to attempt to uncouple the actions of research support and research publication. A research design service run through an organisation such as the World Federation of Societies of Anaesthesiologists (WFSA) might be a suitable intermediary to help ensure that research is of a suitable quality for publication before submission. Such a body could work closely with journal editors, ethicists, statisticians and clinical academics to offer support to academics from LMICs, without the reliance on high-income country partners or beneficent journal editors. Such a service could help from the very outset with hypothesis generation, study design, ethical approval, research governance, data analysis, writing and submission. Importantly, it could also foster collaborations between LMICs as opposed to between high-income countries and LMIC partners. As ever, the clear barrier is one of funding – without a clear income stream to support it, such a service would place an impossible burden on a membership organisation such as the WFSA. There are data that suggest research is becoming increasingly globalised, with a growing number of countries outside Europe and the USA serving as trial sites, as

pharmaceutical and device companies move phase-2 and -3 trials into LMICs to achieve cost savings of as much as 90% per subject recruited, while avoiding a regulatory environment in HICs which some perceive as burdensome. There is a very clear need for a robust approach to ensuring high ethical standards while encouraging academic cross-fertilisation, and indeed, seeking the views of those who participate in international academic and research partnerships [27, 28].

Re-reading the 1967 publication in *Anaesthesia,* a cynical view might be that very little has changed in the intervening 50 years. Many of the issues highlighted remain the same, and many of the proposed solutions have been tried and found wanting. This would seem unnecessarily gloomy: over the half century we have developed enormous insight into the potential pitfalls of international aid; established productive partnerships between UK anaesthetists and LMIC partners across the world; and built structures to facilitate an international research community of equals. The challenge of the next 50 years will be to deliver on this promise.

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TB is President of the World Anaesthesia Society, an external advisor for the Tropical Health and Education Trust (THET) Global Surgery and Anaesthesia Technical Taskforce, sits on the Education Board of the Lifebox Foundation, and is a Committee member of Cambridge Global Health Partnerships. AV is an Editor of *Anaesthesia*.

References

1. Kwikiriza A, JKiwanuka JK, Firth PG, Hoeft MA, Modest VE, Ttendo SS. The analgesic effects of intrathecal morphine in comparison with ultrasound-guided transversus abdominis plane block after caesarean section: a randomised controlled trial at a Ugandan regional referral hospital. *Anaesthesia* 2018; https://doi.org/10.1111/anae.14467
2. Association of Anaesthetists. Aid to developing countries. *Anaesthesia* 1967; **22**: 276–81.
3. Farman JV. Anaesthetic problems facing developing countries. *Anaesthesia* 1967; **22**: 714–15.
4. Walker IA, Wilson IH. Anaesthesia in developing countries – a risk for patients. *Lancet* 2008; **371**: 968–9.
5. Hodges S, Walker I, Bösenberg A. Paediatric anaesthesia in developing countries. *Anaesthesia* 2007; **62**: 26–31.
6. Towey RM, Ojara S. Intensive care in the developing world. *Anaesthesia* 2007; **62**: 32–7.
7. Hodges SC, Mijumbi C, Okello M, McCormick BA, Walker IA, Wilson IH. Anaesthesia services in developing countries: defining the problems. *Anaesthesia* 2007; **62**: 4–11.
8. Hewitt-Smith A, Bulamba F, Ttendo S, Pappenheim K, Walker IA, Smith AF. A mixed-methods evaluation of the Association of Anaesthetists of Great Britain and Ireland Uganda Fellowship Scheme. *Anaesthesia* 2018; **73**: 284–94.
9. Gatrad AR, Gatrad S, Gatrad A. Equipment donation to developing countries. *Anaesthesia* 2007; **62**: 90–5.
10. Albert V, Mndolo S, Harrison EM, O'Sullivan E, Wilson IH, Walker IA. Lifebox pulse oximeter implementation in Malawi: evaluation of educational outcomes and impact on oxygen desaturation episodes during anaesthesia. *Anaesthesia* 2017; **72**: 686–93.
11. Lilaonitkul M, Kwikiriza A, Ttendo S, et al. Implementation of the WHO Surgical Safety Checklist and surgical swab and instrument counts at a regional referral hospital in Uganda – A quality improvement project. *Anaesthesia* 2015; **70**: 1345–55.
12. Zachariah R, Tayler-Smith K, Ngamvithayapong-Yana J, et al. The published research paper: is it an important indicator of successful operational research at programme level? *Tropical Medicine and International Health* 2010; **15**: 1274–7.
13. Bainbridge D, Martin J, Arango M, Cheng D. Perioperative and anaesthetic-related mortality in developed and developing countries: a systematic review and meta-analysis. *Lancet* 2012; **380**: 1075–81.
14. Ouro-Bang'na Maman AF, Tomta K, Ahouangbévi S, Chobli M. Deaths associated with anaesthesia in Togo, West Africa. *Tropical Doctor* 2005; **35**: 220–2.
15. Moonesinghe SR, Peden CJ. Theory and context: putting the science into improvement. *British Journal of Anaesthesia* 2017; **118**: 482–4.
16. Wagstaff DT, Bedford J, Moonesinghe SR. Improvement science in anaesthesia. *Current Anesthesiology Reports* 2017; **7**: 432–9.
17. Crowe S, Brown K, Tregay J, et al. Combining qualitative and quantitative operational research methods to inform quality improvement in pathways that span multiple settings. *BMJ Quality and Safety* 2017; **26**: 641–52.
18. Monks T. Operational research as implementation science: definitions, challenges and research priorities. *Implementation Science* 2016; **11**: 81.
19. Bonell C, Oakley A, Hargreaves J, Strange V, Reese R. Assessment of generalisability in trials of health interventions: suggested framework and systematic review. *British Medical Journal* 2006; **333**: 346–9.
20. Mhyre JM. The critical role of obstetric anaesthesia in low-income and middle-income countries. *Lancet Global Health* 2016; **4**: e290–1.
21. Aveling E-L, Zegeye DT, Silverman M. Obstacles to implementation of an intervention to improve surgical services in an Ethiopian hospital: a qualitative study of an international health partnership project. *BMC Health Services Research* 2016; **16**: 393.
22. Nakimuli A, Chazara O, Hiby SE, et al. A *KIR B* centromeric region present in Africans but not Europeans protects pregnant women from pre-eclampsia. *Proceedings of the National Academy of Science of the USA* 2015; **112**: 845–50.
23. Dickert N, Wendler D. Ancillary care obligations of medical researchers. *Journal of the American Medical Association* 2009; **302**: 424–8.
24. Martiniuk ALC, Manouchehrian M, Negin JA, Zwi AB. Brain Gains: a literature review of medical missions to low and middle-income countries. *BMC Health Services Research* 2012; **12**: 134.
25. National Institute for Health Research. Global Health Research. 2018. https://www.nihr.ac.uk/funding-and-support/global-health-research (accessed 19/10/2018).
26. UK Research and Innovation. Global Challenges Research Fund. 2018. https://www.ukri.org/research/global-challenges-research-fund (accessed 19/10/2018).
27. Glickman SW, McHutchison JG, Peterson ED, et al. Ethical and scientific implications of the globalization of clinical research. *New England Journal of Medicine* 2009; **360**: 816–23.
28. Elobu AE, Kintu A, Galukande M, et al. Evaluating international global health collaborations: perspectives from surgery and anesthesia trainees in Uganda. *Surgery* 2014; **155**: 585–92.

